## REMARKS

In the Claims

Claims 1 and 109 have been amended.

Support for the amendments to claims 1 and 109 is to be found in the specification at paragraphs [16], [174-180], (page 5, lines 11-15, page 28, lines 30-34 and page 29, lines 1-20 of application as filed) and table 4, where different electrochemical characteristics are disclosed and where the different electrochemical characteristics being a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe are disclosed.

No new matter has been added by these amendments.

Applicants respectfully request entry of the present amendment.

Claim Rejections under 35 USC § 103(a)

1) The Examiner has rejected claims 1- 9, 11-18, 20-25, 43-45, 91-101, 109-116, and 119-129 under 35 USC § 103(a) as being unpatentable over Calzone et al. (Methods in Enzymology (1987) vol. 152, pp. 611-632) in view of Clinical Micro Sensors, Inc. (CMS; WO01/06016, published January 25, 2001).

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 148 USPQ 459, 467 (S.Ct. 1966).

> "In determining obviousness, "[i]t is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure." By way of contrast, in determining novelty, a showing that the "prior art reference cited as anticipating a claimed invention. . .lack[ed] the characteristics of the claimed invention. . .would in fact negate the assertion that the claimed invention was described in the prior art." In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).

> "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)

2) Applicants have amended claim 1 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the oligonucleotide probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively degrading hybridized oligonucleotide probe, the degrading resulting in degraded oligonucleotide probe; and electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe and wherein the electrochemical activity of the electrochemically active marker correlates with the size of the degraded and the non-degraded oligonucleotide probe, the method resulting in probing for the nucleic acid.".

Applicants have amended claim 109 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the oligonucleotide probe is able to at least partially hybridize with any complementary target nucleic acid

sequence which may be present in the nucleic acid solution; selectively digesting hybridized oligonucleotide probe using a duplex specific exonuclease; and electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe and wherein the electrochemical activity of the electrochemically active marker correlates with the extent of digestion of the oligonucleotide probe, the method resulting in probing for the nucleic acid".

With respect to claim 1, Applicants respectfully submit that neither Calzone et al. nor CMS teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

With respect to claim 109, Applicants respectfully submit that neither Calzone et al, nor CMS teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the

degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Applicants submit that Calzone et al. do not teach using electrochemically active markers that exhibit different electrochemical characteristics as recited in claim 1 and which are disclosed in the specification at pages 26-32 (paragraphs [143] to [219]) where the electrochemical activity of different oligonucleotide probes labeled with electrochemically active markers and then digested or degraded are compared with that of non-degraded or non-degraded probes (see Examples 4 through 5)

Applicants submit that CMS does not teach using electrochemically active markers that exhibit different electrochemical characteristics as recited in claim 1 and which are disclosed in the instant specification at pages 26-32 (paragraphs [143] to [219]) where the different electrochemical characteristics (electrochemical activity) of different oligonucleotide probes labeled with electrochemically active markers and then digested or degraded are compared with that of non-digested or non-degraded probes (see Examples 4 through 5, pages 25-32).

Applicants further submit that CMS does not teach nor suggest electrochemically determining the electrochemical activity of non-degraded or non-digested oligonucleotide probe.

With regard to claims 2 and 112, the Examiner stated that the presence of non-degraded probe of Calzone et al. teaches the presence of the nucleic acid, Applicants respectfully submit that the presence of a non-degraded probe using the method taught be Calzone et al. would suggest to one of skill in the art the absence of nucleic acid. Applicants submit that non-degraded probe would be present if there was no target nucleic acid to bind to and therefore no degradation by the enzyme could be initiated. Applicants submit that at Figure 2a, lane 2, Calzone et al. teach that non-degraded probe (540-nucleotide gene fragment as disclosed in the first line of the figure legend on page 625) is present in the absence of nucleic acid (viz. in the presence of yeast RNA that does not comprise the nucleic acid of interest; used as a negative control). Applicants submit that the amounts of

non-degraded probe in lanes 1 and 2 cannot be distinguished by eye due to the amount of excess probe used in the assay and therefore the presence of non-degraded probe cannot be predicted to teach the presence of nucleic acid.

With regard to claims 3, 94, and 113, the Examiner stated that Calzone et al. teach in Figure 2 the relative portions of degraded and non-degraded probes as the 520 base primary transcript and the 75 base mature mRNA. Applicants submit that the Examiner has misunderstood the assay process as outlined in the legend for Figure 2.

Applicants submit, as noted above, that the non-degraded probe is the 540-nucleotide gene fragment as illustrated in Figure 2b and shown as present in the gel as the major autoradiographic band common to the top of both gel lanes of Figure 2a.

Applicants submit that the two other transcripts identified in Figure 2, "Primary transcript" at 520 nucleotides and "mature mRNA" at 75 nucleotides, are the end product of the reaction, representing degraded fragments of the probe that had initially hybridized to either un-processed hnRNA (Intron and Exon I: 520 nt duplex hybrid) or processed mRNA (Exon I alone: 75 nt duplex hybrid) and that where then degraded by removal of the overhangs by a single-strand-specific nuclease.

Where, as the Examiner states at page 4, lines 11-14 of the instant Office action, CMS teaches that ETMs allow amplification of signal resulting in sensitive assays (see CMS page 54, lines 7-50 (sic)) and this provides for extremely specific and sensitive probes, which may detect target sequences without removal of unhybridized probe, Applicants submit that the signal so amplified is the result of using multiple and/or pluralities of EMTs (CMS at page 54, lines 8-16) and is not due to the different electrochemical characteristics of different oligonucleotide probes labeled with electrochemically active markers as claimed in claim 1 and as disclosed in the specification in Examples 4 and 5, Table 4 and Figures 8 through 13.

Therefore, Applicants submit that both the teachings of Calzone et al. and CMS "lack[ed] the characteristics of the claimed invention" (In re Mills, 16 USPQ2d 1430 (Fed. Cir.

1990). In addition, Applicants submit that the different electrochemical characteristics of the different oligonucleotide probes labeled with electrochemically active markers as disclosed could not have been predicted by one of skill in the art combining the teachings of Calzone et al. and CMS at the time the invention was made (*Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

Applicants further submit that one of skill in the art would not have been motivated to combine the teachings of Calzone et al. and CMS to improve the method of Calzone et al. and which would then have enabled the skilled artisan to determine the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Applicants further submit that even if there were motivation to combine the teachings of Calzone et al. and CMS, the combined teachings could not have enabled the skilled artisan to determine the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Applicants draw the Examiner's attention to the Specification at page 5, lines 11-15, (paragraph [16] of the US Application as published) where Applicants state: "(t)he present invention is based upon the observation that an electrochemically active marker such as

metallocene exhibits different electrochemical characteristics depending upon whether or not it is attached to a nucleotide, whether or not that nucleotide is incorporated into an oligonucleotide or not, and the length of any such oligonucleotide". Applicants submit that this property would not have been predicted by one of skill in the art and the property was unexpected.

The Examiner stated in the instant Office action (Page 9, lines 8-9) that the arguments above had not been considered persuasive as they are arguments of counsel that have not been supported by evidence. Applicants submit that claim 1 now recites particular different electrochemical characteristics that are supported by the specification at paragraphs [16], [174-180], and table 4. Applicants further submit that evidence for the different electrochemical characteristics is to be found in Example 4(h) (where Applicants disclose that "(n)o significant changes to the ferrocene signal were observed when comparing heat denatured enzyme and no enzyme controls", see page 29, lines 14-15; paragraph 179), in Table 4 (pages 28-30), and in Figures 9, 8, 6,and 10. In all cases, using different oligonucleotides, the peak height upon digestion or degrading the oligonucleotide increased by more than 215%, a characteristic that would not and could not have been predicted by combining the references of Calzone et al. and CMS.

Applicants submit that the record contains no evidence that a skilled artisan would have considered modification of the methods of Calzone et al. by use of the ETM labels and nucleases and methods of detecting ETM labels taught by CMS to determine the activity of an electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Regarding claim 1, therefore, Applicants submit that the prior art and the claims at issue are different, the Calzone et al. and Clinical Micro Sensors, Inc. references lack the characteristics of the claimed invention, and therefore that claim 1 is not unpatentable over Calzone et al. in view of Clinical Micro Sensors, Inc. Applicants further submit that dependent claims 2-18, 20-25, 43-45, and 91-101 are therefore also not unpatentable over Calzone et al. in view of Clinical Micro Sensors, Inc.

Regarding claim 109, therefore, Applicants submit that the prior art and the claims at issue are different and therefore that claim 109 is not unpatentable over Calzone et al. in view of Clinical Micro Sensors, Inc. Applicants further submit that dependent claims 110-116, and 119-129 are therefore also not unpatentable over Calzone et al. in view of Clinical Micro Sensors, Inc.

Applicants therefore respectfully request that the Examiner withdraw the rejections of claims 1-18, 20-25, 43-45, 91-101, 109-116, and 119-129 under 35 USC § 103(a).

3) The Examiner has rejected claim 93 under 35 USC § 103(a) as being unpatentable over Calzone et al. (Methods in Enzymology (1987) vol. 152, pp. 611-632) and Clinical Micro Sensors, Inc. (WO01/06016, published January 25, 2001) as applied to claims 1-18, 20-25, 43-45, 91-101, 109-116, and 119-129, and further in view of Nikiforov et al. (US Patent 5,518,900, issued May 21, 1996).

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 148 USPQ 459, 467 (S.Ct. 1966).

> "In determining obviousness, "[i]t is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure." By way of contrast, in determining novelty, a showing that the "prior art reference cited as anticipating a claimed invention. . .lack[ed] the characteristics of the claimed invention. . .would in fact negate the assertion that the claimed invention was described in the prior art." In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).
>
> "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)

4) Applicants have amended claim 1 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the oligonucleotide probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively degrading hybridized oligonucleotide probe, the degrading resulting in degraded oligonucleotide probe; and electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe and wherein the electrochemical activity of the electrochemically active marker correlates with the size of the degraded and the non-degraded oligonucleotide probe, the method resulting in probing for the nucleic acid.".

Applicants respectfully submit that, as recited above, neither Calzone et al. nor CMS teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the

oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

To the extent that claim 93 is dependent upon claim 1 through dependent claims 12 and 11, Applicants' amendments to claim 1 and remarks as presented above are believed to overcome the rejection under 35 USC § 103(a) as being unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. and further in view of Nikiforov et al.

With respect to claim 1, Applicants respectfully submit that neither Calzone et al. nor CMS teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Applicants also submit that Nikiforov et al. do not teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Applicants submit that the prior art and the claims at issue are different, the Calzone et al., Clinical Micro Sensors, Inc., and Nikiforov et al. references lack the characteristics of the claimed invention, and therefore that claim 93, being dependent upon claim 1, is not unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. in view of Nikiforov et al.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claim 93 under 35 USC § 103(a).

5) The Examiner has rejected claims 102-105 and 130-133 under 35 USC § 103(a) as being unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. (WO01/06016, published January 25, 2001) as applied to claims 1-18, 20-25, 43-45, 91-101, 109-116, and 119-129, in view of Heller et al. (US Patent 5,605,622, issued February 25, 1997).

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 148 USPQ 459, 467 (S.Ct. 1966).

> "In determining obviousness, "[i]t is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure." By way of contrast, in determining novelty, a showing that the "prior art reference cited as anticipating a claimed invention. . .lack[ed] the characteristics of the claimed invention. . .would in fact negate the assertion that the claimed invention was described in the prior art." In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).

> "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)

6) Applicants have amended claim 1 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the oligonucleotide

probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively degrading hybridized oligonucleotide probe, the degrading resulting in degraded oligonucleotide probe; and electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe and wherein the electrochemical activity of the electrochemically active marker correlates with the size of the degraded and the non-degraded oligonucleotide probe, the method resulting in probing for the nucleic acid.".

Applicants have amended claim 109 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the oligonucleotide probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively digesting hybridized oligonucleotide probe using a duplex specific exonuclease; and electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe and wherein the electrochemical activity of the electrochemically active marker correlates with the extent of digestion of the oligonucleotide probe, the method resulting in probing for the nucleic acid".

To the extent that claims 102-105 are dependent upon claim 1, Applicants' amendments to claim 1 and remarks as presented above are believed to overcome the rejection under 35 USC § 103(a) as being unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. and further in view of Heller et al.

With respect to claim 1, Applicants respectfully submit that neither Calzone et al. nor CMS teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

To the extent that claims 130-133 are dependent upon claim 109, Applicants' amendments to claim 109 and remarks as presented above are believed to overcome the rejection under 35 USC § 103(a) as being unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. and further in view of Heller et al.

With respect to claim 109, Applicants respectfully submit that neither Calzone et al, nor CMS teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Applicants have considered the "Heller et al." reference cited by the Examiner (US Patent 5,605,622) and respectfully point out that US Patent 5,605,622 as cited in a previous Office action (Office action mailed June 14, 2007, Notice of References Cited, copy attached) is in fact a patent to Ferraro et al. and appears to be drawn to art relating to swimming pool vacuum systems, an unrelated art. Applicants are therefore unable to find or study the Heller reference as disclosed by the Examiner in prior Office actions to date.

Applicants believe that the citation is an error. Applicants respectfully request clarification as to the proper citation of "Heller et al".

Applicants also submit that US Patent 5,605,622 does not teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Applicants submit that the prior art and the claims at issue are different, the Calzone et al., Clinical Micro Sensors, Inc., and US Patent 5,605,622 references lack the characteristics of the claimed invention, and therefore that claims 102-105 and claims 130-133, being dependent upon claim 1 and claim 109 respectively, are not unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. in view of US Patent 5,605,622 ("Heller et al.").

Applicants therefore respectfully request that the Examiner withdraw the rejections of claims 102-105 and 130-133 under 35 USC § 103(a).

7) The Examiner has rejected claims 19, 117, and 118 under 35 USC § 103(a) as being unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. (WO01/06016, published January 25, 2001) as applied to claims 1-18, 20-25, 43-45, 91-101, 109-116, and 119-129, in view of Hall et al. (US Patent 5,994,069, issued November 30, 1999).

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 148 USPQ 459, 467 (S.Ct. 1966).

> "In determining obviousness, "[i]t is not pertinent whether the prior art device possesses the functional characteristics of the claimed invention if the reference does not describe or suggest its structure." By way of contrast, in determining novelty, a showing that the "prior art reference cited as anticipating a claimed invention. . .lack[ed] the characteristics of the claimed invention. . .would in fact negate the assertion that the claimed invention was described in the prior art." In re Mills, 16 USPQ2d 1430 (Fed. Cir. 1990).

> "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)

8) Applicants have amended claim 1 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the oligonucleotide probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively degrading hybridized oligonucleotide probe, the degrading resulting in degraded oligonucleotide probe; and electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different

electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe and wherein the electrochemical activity of the electrochemically active marker correlates with the size of the degraded and the non-degraded oligonucleotide probe, the method resulting in probing for the nucleic acid.".

Applicants have amended claim 109 to recite "A method of probing for a nucleic acid comprising: contacting a nucleic acid solution with an oligonucleotide probe labeled with an electrochemically active marker; providing conditions at which the oligonucleotide probe is able to at least partially hybridize with any complementary target nucleic acid sequence which may be present in the nucleic acid solution; selectively digesting hybridized oligonucleotide probe using a duplex specific exonuclease; and electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe and wherein the electrochemical activity of the electrochemically active marker correlates with the extent of digestion of the oligonucleotide probe, the method resulting in probing for the nucleic acid".

To the extent that claim 19 is dependent upon claim 1, Applicants' amendments to claim 1 and remarks as presented above are believed to overcome the rejection under 35 USC § 103(a) as being unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. and further in view of Hall et al.

With respect to claim 1, Applicants respectfully submit that neither Calzone et al. nor CMS teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the

electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

To the extent that claims 117 and 118 are dependent upon claim 109, Applicants' amendments to claim 109 and remarks as presented above are believed to overcome the rejection under 35 USC § 103(a) as being unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. and further in view of Hall et al.

With respect to claim 109, Applicants respectfully submit that neither Calzone et al, nor CMS teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Applicants also submit that Hall et al. do not teach a method of probing for a nucleic acid comprising electrochemically determining the activity of the electrochemically active marker, wherein the electrochemical activity of the electrochemically active marker exhibits different electrochemical characteristics depending on (a) whether or not it is attached to a nucleotide, (b) whether or not that nucleotide is incorporated into the oligonucleotide or not, and (c) the length of the oligonucleotide, and wherein the different electrochemical characteristics are a change to the activity of the electrochemically active

marker of the degraded oligonucleotide probe compared with the activity of the electrochemically active marker of non-degraded oligonucleotide probe.

Applicants submit that the prior art and the claims at issue are different, the Calzone et al., Clinical Micro Sensors, Inc., and Hall et al. references lack the characteristics of the claimed invention, and therefore that claim 19, and claims 117 and 118, being dependent upon claims 1 and 109 respectively, are not unpatentable over Calzone et al. and Clinical Micro Sensors, Inc. in view of Hall et al.

Applicants therefore respectfully request that the Examiner withdraw the rejections of claims 19, 117, and 118 under 35 USC § 103(a).

## CONCLUSION

With these arguments, Applicants believe that the application is in condition for allowance. If the US Patent Office believes that communication would further the prosecution of this application, then the appropriate US Patent Office personnel are invited to contact the Applicants' below-signed representative at their earliest convenience.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Bell & Associates Deposit Account No. 50-3194.

Dated and signed:

21st October 2009

Matthew Kaser, D.Phil.
Reg. No. 44,817

Bell & Associates,
58 West Portal Avenue, # 121,
San Francisco, California 94127
Tel: (510) 537-2040
Fax: (415) 276-6040
mkaser@bell-iplaw.com

# Notice of References Cited

| 10/506,958 | Reexamination BRAVEN ET AL. | |
|---|---|---|
| Examiner Steven C. Pohnert | Art Unit 1634 | Page 1 of 1 |

**U.S. PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Name | Classification |
|---|---|---|---|---|---|
| * | A | US-5,994,069 | 11-1999 | Hall et al. | 435/6 |
| * | B | US-5,605,622 | 02-1997 | Ferraro, Michael J. | 210/167.12 |
| * | C | US-5,770,370 | 06-1998 | Kumar, Rajan | 435/6 |
| * | D | US-5,518,900 | 05-1996 | Nikiforov et al. | 435/91.1 |
| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

**FOREIGN PATENT DOCUMENTS**

| * | | Document Number Country Code-Number-Kind Code | Date MM-YYYY | Country | Name | Classification |
|---|---|---|---|---|---|---|
| | N | WO-01/06016 | 01-2001 | WO | Clinical Micro Sensors | 435/6 |
| | O | | | | | |
| | P | | | | | |
| | Q | | | | | |
| | R | | | | | |
| | S | | | | | |
| | T | | | | | |

**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
|---|---|---|
| | U | |
| | V | |
| | W | |
| | X | |

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.